REVIEW ARTICLE

John A. Jarcho, M.D., *Editor*

Lipid Management for the Prevention of Atherosclerotic Cardiovascular Disease

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In 1961, the investigators involved in the Framingham Heart Study identified serum cholesterol as one of the "factors of risk" for coronary heart disease.[1] Since then, numerous epidemiologic studies and randomized clinical trials have established that an elevated level of low-density lipoprotein (LDL) cholesterol is a major contributor to atherosclerotic cardiovascular disease.[2,3] As a consequence, the management of serum cholesterol levels has become a central objective in the effort to prevent cardiovascular events. The currently used therapies with demonstrated efficacy (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) predominantly target the apolipoprotein B–associated lipoproteins reflected in levels of LDL cholesterol, non–high-density lipoprotein cholesterol (non-HDL cholesterol), and triglycerides (Fig. 1).

The most recent guidelines for cholesterol management put forward by the American College of Cardiology–American Heart Association (ACC–AHA) were published in 2018 (Fig. 2).[4] In 2019, the ACC–AHA published guidelines for the primary prevention of cardiovascular disease, carrying forward recommendations for risk estimation and lipid management from the 2018 guidelines on cholesterol management.[5] Informed by these new guidelines and other recent advances in treatment, this review is intended to summarize current methods of managing serum lipid levels for the prevention of atherosclerotic cardiovascular disease.

Lifestyle Management

The foundation for managing serum cholesterol is the facilitation of a healthy lifestyle (which includes diet) across a person's life span.[5,6] Even persons whose genetic profile puts them at increased risk for coronary heart disease can reduce their risk by up to 50% through changes in lifestyle.[7] Maintenance of a normal weight and blood sugar level, reduction in the intake of simple sugars and refined carbohydrates, and increases in physical activity all improve lipid levels and provide other healthful benefits[4,8,9] and should be undertaken regardless of whether pharmacotherapy is also recommended. Dietary and other changes in lifestyle recommended for the management of lipid levels are discussed further in the Supplementary Appendix.

LDL Cholesterol Level and Risk

The direct relationship between LDL cholesterol level and the risk of atherosclerotic cardiovascular disease[10] has led to the simple recommendation that "lower is better." However, measurement of LDL cholesterol levels alone is not sufficient to assess cardiovascular risk. Approximately 40% of persons with coronary heart disease have a total cholesterol level of less than 200 mg per deciliter (5.2 mmol

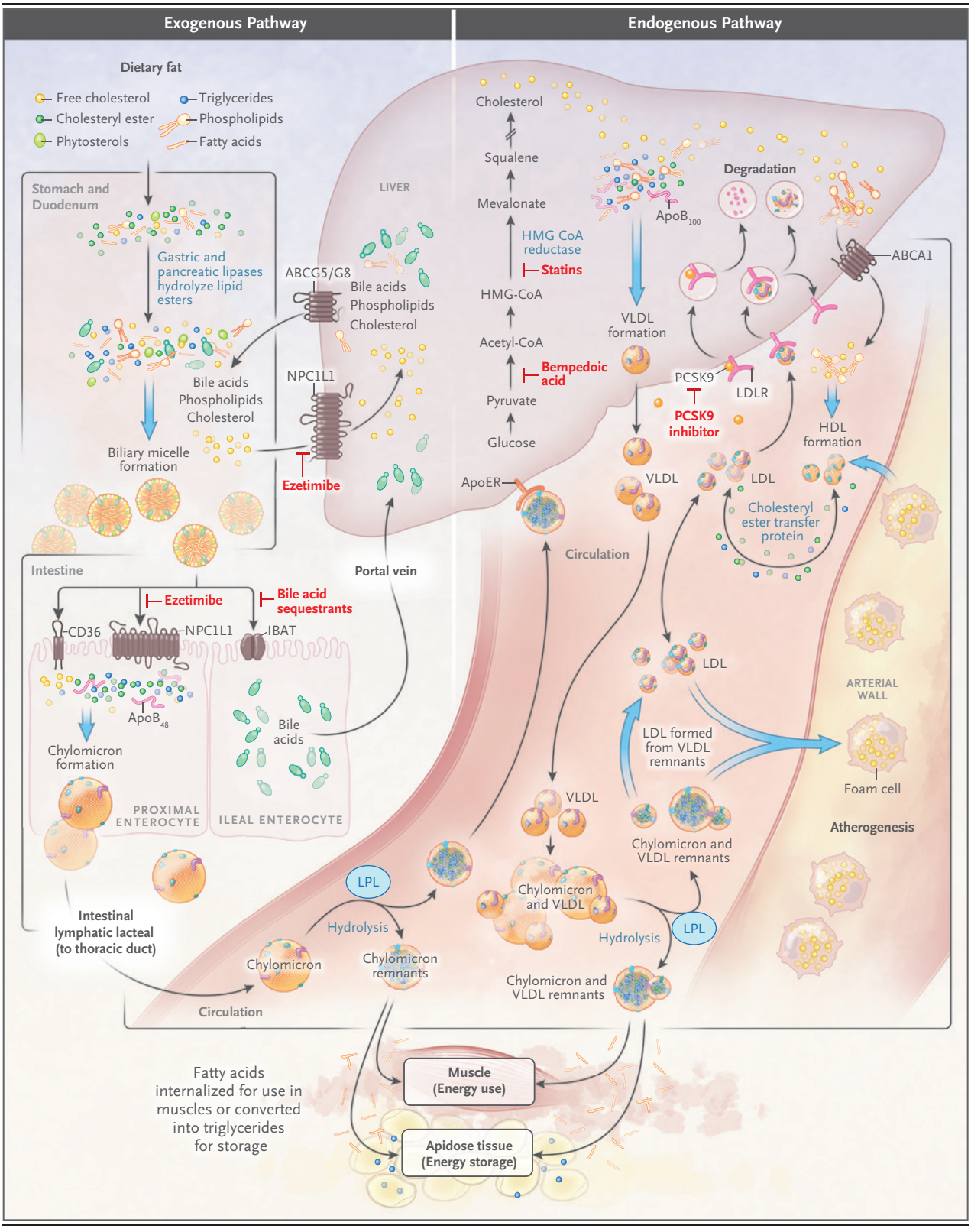
Exogenous Pathway
Endogenous Pathway
Dietary fat
Free cholesterol
Cholesteryl ester
Phytosterols
Triglycerides
Phospholipids
Fatty acids
Stomach and Duodenum
Gastric and pancreatic lipases hydrolyze lipid esters
LIVER
ABCG5/G8
Bile acids
Phospholipids
Cholesterol
NPC1L1
Bile acids
Phospholipids
Cholesterol
Biliary micelle formation
Ezetimibe
Intestine
Ezetimibe
Bile acid sequestrants
CD36
NPC1L1
IBAT
ApoB48
Chylomicron formation
PROXIMAL ENTEROCYTE
ILEAL ENTEROCYTE
Bile acids
Portal vein
Intestinal lymphatic lacteal (to thoracic duct)
Chylomicron
Circulation
LPL
Hydrolysis
Chylomicron remnants
Cholesterol
Squalene
Mevalonate
HMG CoA reductase
Statins
HMG-CoA
Acetyl-CoA
Bempedoic acid
Pyruvate
Glucose
ApoER
ApoB100
Degradation
VLDL formation
PCSK9
LDLR
PCSK9 inhibitor
ABCA1
HDL formation
VLDL
LDL
Cholesteryl ester transfer protein
Circulation
LDL
ARTERIAL WALL
LDL formed from VLDL remnants
Foam cell
Atherogenesis
VLDL
Chylomicron and VLDL remnants
Chylomicron and VLDL
LPL
Hydrolysis
Chylomicron and VLDL remnants
Fatty acids internalized for use in muscles or converted into triglycerides for storage
Muscle (Energy use)
Apidose tissue (Energy storage)

Figure 1 (facing page). Lipid Metabolism and Targets for Pharmacotherapy.
The gastric lipid pool contains ingested free cholesterol, cholesterol esters, phytosterols, triglycerides, phospholipids, and fatty acids (see exogenous pathway). Gastric and pancreatic lipases hydrolyze lipid esters. Bile acids, phospholipids, and cholesterol are secreted by hepatocytes by means of specific transporters (ABCG5, ABCG8, and ABCB11) into the biliary system. Conversely, the Niemann–Pick C1-like 1 (NPC1L1) protein facilitates the transfer of cholesterol from bile back into hepatocytes. Ezetimibe blocks biliary NPC1L1. Bile acids and lipids generate complex biliary micelles that transport the lipids to intestinal microvilli absorption sites. NPC1L1 facilitates the entry of cholesterol into enterocytes, a step that is also blocked by ezetimibe. Fatty-acid transport proteins such as CD36 regulate the absorption of de-esterified fatty acids and monoacylglycerols. Once freed from micelles, bile acids are reabsorbed by the ileal bile-acid transporter (IBAT) and released into the portal circulation for return to the liver. Bile-acid sequestrants block the reabsorption of bile acids in the ileum. Cholesterol and triglycerides are assembled into chylomicrons through a synthesis pathway that relies on microsomal triglyceride transfer protein and apolipoprotein B_{48}. Chylomicrons are secreted into the intestinal lymphatic system before entering the circulation at the thoracic duct. Triglyceride-rich lipoproteins, such as chylomicrons and very-low-density lipoproteins (VLDL), undergo lipolysis (hydrolysis of core triglycerides and surface phospholipids) through the interaction of apolipoprotein cholesterol-II and lipoprotein lipase (LPL) in the muscle and adipocyte vascular beds, allowing fatty acids to be internalized and used in muscles as an energy source or synthesized into triglycerides for energy storage in adipocytes. The action of LPL on chylomicrons reduces their fatty-acid content and results in the production of chylomicron remnants; similarly, VLDLs are converted into VLDL remnants (intermediate density lipoproteins [IDLs]).

Hepatic synthesis of cholesterol (see endogenous pathway) begins with the conversion of glucose to pyruvate by means of a synthesis pathway that relies on the substrate acetyl coenzyme A (CoA), which is created during the Krebs cycle. β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase is the rate-limiting enzyme in this pathway, forming squalene and several sterol intermediates and ultimately cholesterol. Statins inhibit HMG-CoA reductase. Bempedoic acid is a prodrug that is converted by the very-long-chain acyl-CoA synthetase-1 (an enzyme present in hepatocytes but not myocytes) into an active metabolite that reduces the production of acetyl CoA in hepatocytes by inhibiting ATP citrate lyase, thereby reducing cholesterol metabolism in the liver. By means of a synthesis pathway that relies on the action of microsomal triglyceride transfer protein, triglyceride joins with cholesterol, cholesteryl ester, phospholipids, and apolipoprotein B-100 to assemble into particles of VLDL cholesterol, which are secreted into the circulation. High-density lipoproteins (HDLs) are formed from the efflux of cholesterol and phospholipids (by means of the membrane transporter ATP-binding cassette transporter A1 [ABCA1]) into apolipoprotein A-I (apoA-I) or smaller HDL species. The efflux of cholesterol from arterial-wall foam cells to HDL cholesterol is a crucial and specific part of HDL cholesterol function called macrophage reverse cholesterol transport. Particles of low-density lipoprotein (LDL) cholesterol bind to and are cleared from plasma by LDL cholesterol receptors. The liver synthesizes and secretes proprotein convertase subtilisin–kexin type 9 (PCSK9), which binds to LDL cholesterol receptors, causing receptor catabolism when internalized by endosomes and lysosomes. PCSK9 inhibitors block this process. Atherogenesis occurs when apolipoprotein B–containing particles (including LDL cholesterol molecules, which are the most numerous, and chylomicron and VLDL remnants) enter the arterial wall, undergo oxidation, and are internalized by macrophages, creating foam cells.

per liter).[11] Conversely, many persons with a moderate elevation in LDL cholesterol level never have a clinical cardiovascular event. In the 2013 ACC–AHA guidelines on the management of cholesterol,[12] there was a movement away from targeting specific LDL cholesterol values and toward a focus on treatment of persons at the greatest absolute risk of cardiovascular disease with high-intensity statins.[12] As cardiovascular risk increases, so does the absolute benefit of treatment with therapies proved to lower LDL cholesterol levels.[13,14] Since publication of the 2013 guidelines, additional findings from randomized clinical trials[15,16] have provided further support for the concept that the magnitude of event reduction is proportional to the degree to which LDL cholesterol is lowered.[10,13] Thus, both the absolute risk and the magnitude of the reduction in LDL cholesterol level achieved are important. The 2018 cholesterol guidelines bring back recommendations for specific percentage reductions in LDL cholesterol levels as well as the use of LDL cholesterol thresholds for the addition of nonstatin therapy to statins in patients at high risk for atherosclerotic cardiovascular disease (Fig. 2).[4]

SHARED DECISION MAKING

One critical feature of both the 2013 and 2018 cholesterol guidelines is the recommendation that clinicians conduct a general discussion of cardiovascular risk with patients before initiating a statin.[4,12] This shared decision-making process should involve a review of the patient's major risk factors for cardiovascular disease and the patient's estimated level of risk within the next 10 years. The adoption of a heart-healthy lifestyle should be encouraged and the evidence base for lipid-lowering therapy discussed.[17] The conversation should also review the patient's concerns and preferences regarding initiation of preventive pharmacotherapy as well as the potential for adverse effects from therapy.[17]

LIPID MANAGEMENT IN PRIMARY PREVENTION

As a starting point to guide treatment decisions, the 2018 and 2019 guidelines[4,5] recommend use

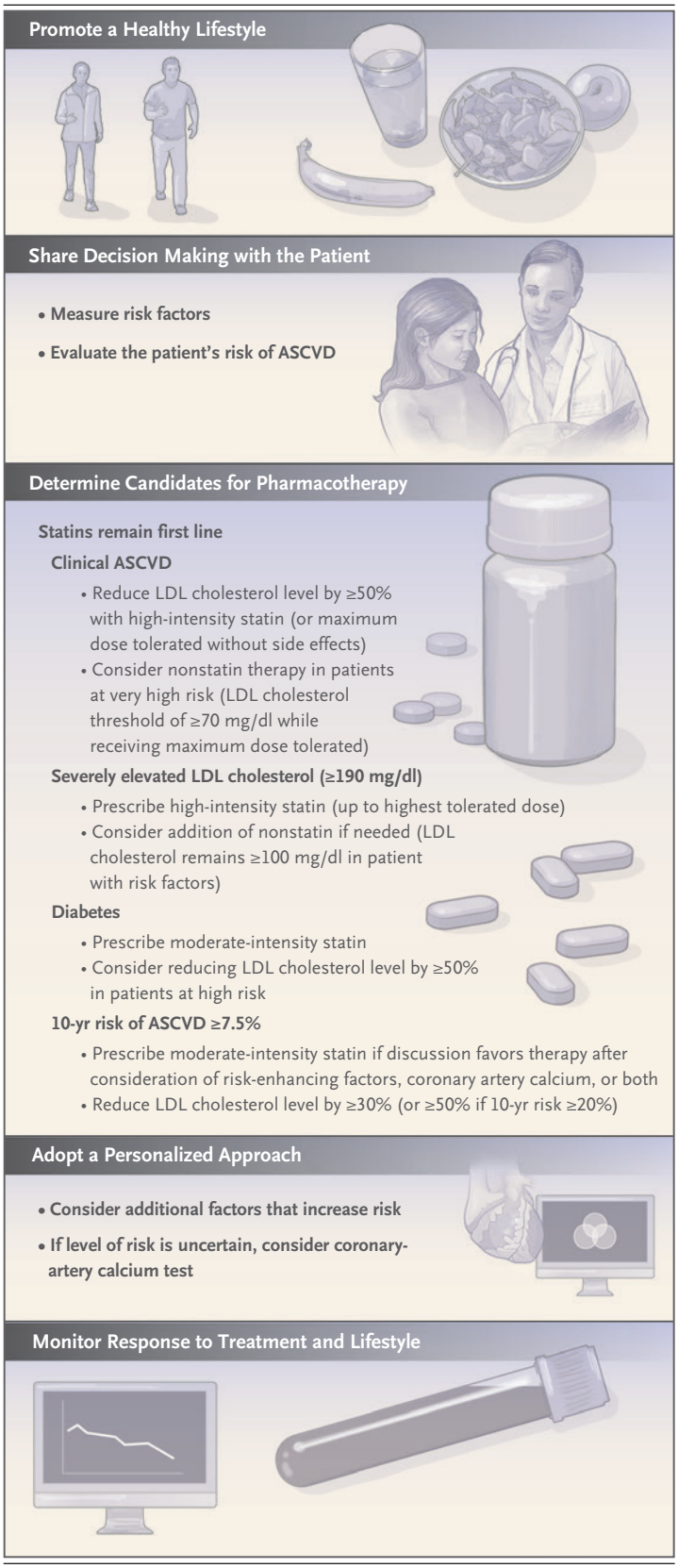

Figure 2. Five Key Points from the 2018 ACC–AHA Guidelines.

A healthy lifestyle is appropriate for all patients as part of the management of cardiovascular risk, including adequate physical activity and a healthy diet. Decisions regarding cardiovascular risk management should be shared between clinician and patient, including interpretation of the patient's 10-year risk of atherosclerotic cardiovascular disease. Recommendations for pharmacotherapy are based on the patient's individual risk profile and clinical characteristics. Statins remain the first-line agents, but for patients with clinical atherosclerotic cardiovascular disease at very high risk or for patients with severely elevated LDL cholesterol levels, nonstatin agents, such as ezetimibe and PCSK9, may be considered. Recommendations for statin therapy also include patients 40 to 75 years of age with a level of LDL cholesterol that is higher than 69 mg per deciliter who have diabetes or who have a 10-year risk of atherosclerotic cardiovascular disease equal to or greater than 7.5%. Additional considerations should be made for younger or older adults. After calculation of the patient's 10-year risk of atherosclerotic cardiovascular disease, risk assessment can be individualized by considering any risk-enhancing factors and the patient's coronary-artery calcium score, if measured. The patient's therapeutic response should continue to be monitored over time.

of the ACC–AHA Risk Calculator to estimate the risk of atherosclerotic cardiovascular disease within 10 years (www.cvriskcalculator.com/).[18] The calculator is intended for adults 40 to 75 years of age who do not have diabetes and whose LDL cholesterol level is 70 mg per deciliter (1.8 mmol per liter) or higher but lower than 190 mg per deciliter (4.9 mmol per liter). After risk estimation, patients can be categorized according to their risk of disease at 10 years: low (<5%), borderline (5 to <7.5%), intermediate (≥7.5 to <20%), or high (≥20%).[4,5] For most patients at low risk for disease, reinforcement of lifestyle changes alone is often sufficient. For those at high risk, the use of a high-intensity statin to reduce the LDL cholesterol level by 50% or more is recommended in combination with adoption of a healthy lifestyle.[4,5] For those at intermediate risk, the initiation of a moderate-intensity statin to reduce the LDL cholesterol level by 30% or more is recommended along with adoption of a healthy lifestyle.[4,5]

The presence of risk-enhancing factors favors the initiation or intensification of statin therapy in patients at intermediate risk and justifies the initiation of therapy among adults with borderline risk.[4,5] These risk-enhancing factors include a history of preeclampsia, early menopause, rheu-

matologic disease, human immunodeficiency virus infection, a strong family history of premature coronary heart disease, South Asian ancestry, chronic kidney disease, persistently elevated triglyceride levels, a low ankle–brachial index, and elevated levels of high-sensitivity C-reactive protein, lipoprotein(a), or apolipoprotein B.[4,5]

The 2018 and 2019 ACC–AHA guidelines recognize that the benefits of lipid pharmacotherapy remain uncertain in persons whose risk of atherosclerotic cardiovascular disease at 10 years is 5 to <20%.[4,5] Among patients at intermediate risk and selected patients with borderline risk for disease, it may be reasonable to measure the atherosclerosis burden by assessing the coronary-artery calcium score with computed tomography (without administration of contrast material) to further refine risk estimation either upward or downward.[4,5,19,20] Statins are generally recommended for persons who have a coronary-artery calcium score that is 100 or higher or who are in the 75th percentile or higher for their age, sex, and race. Statins should also be considered in persons with scores of 1 to 99, particularly if they are 55 years of age or older.[4,5] On the other hand, a coronary-artery calcium score of 0 identifies persons among whom event rates are expected to be well below 7.5% over a 10-year period.[21-24] For such persons, treatment with statins may be withheld or deferred (with the exception of cigarette smokers[25] and persons with familial hypercholesterolemia[26]).

Estimation of lifetime cardiovascular risk may be considered in adults younger than 40 years of age or those 40 to 59 years of age who have a 10-year risk of disease that is less than 7.5% to facilitate the discussion of risk between clinician and patient and to emphasize the value of efforts to maintain a healthy lifestyle.[5] The use of statins for primary prevention in the treatment of patients older than 75 years of age should be considered in the context of a shared decision-making process that factors in the patient's coexisting conditions, life expectancy, and preferences.

In summary, with consideration of risk-enhancing factors and coronary-artery calcium score (if assessed) in the context of a discussion of risk between clinician and patient, the 2018 and 2019 ACC–AHA guidelines allow for personalized treatment decisions regarding lipid management in the primary prevention of atherosclerotic cardiovascular disease.[4,5]

PRIMARY PREVENTION IN SEVERE HYPERCHOLESTEROLEMIA OR DIABETES

For persons with severe primary hypercholesterolemia (an LDL cholesterol level ≥190 mg per deciliter), the likelihood of a familial hypercholesterolemia is increased and there is no need to calculate the 10-year risk of atherosclerotic cardiovascular disease; treatment is recommended to mitigate the substantial lifetime risk of disease. A high-intensity statin (or the maximum tolerated dose) is recommended.[4,5] If the LDL cholesterol level remains 100 mg per deciliter or higher (≥2.6 mmol per liter), it is reasonable to consider treatment with ezetimibe, a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor, or both.

In patients with diabetes who are between 40 and 75 years of age and have an LDL cholesterol level of 70 mg per deciliter or higher, there is also no need to calculate 10-year risk. A moderate-intensity statin should be recommended.[4,5] For patients with diabetes who are at a higher risk for atherosclerotic cardiovascular disease owing to multiple risk factors, it is reasonable to prescribe a high-intensity statin to reduce the LDL cholesterol level by 50% or more.

LIPID MANAGEMENT IN SECONDARY PREVENTION

For patients 75 years of age or younger who have clinical atherosclerotic cardiovascular disease, the LDL cholesterol level should be reduced by at least 50% with the use of a high-intensity statin (or the maximum tolerated dose).[4] If the LDL cholesterol level remains at 70 mg per deciliter or higher with the maximum tolerated dose of statin therapy, it may be reasonable to add ezetimibe. Among patients at very high risk — such as those who have had recent onset of an acute coronary syndrome, multiple events related to atherosclerotic cardiovascular disease, or a prior cardiovascular event with multiple risk factors and those with an LDL cholesterol level ≥70 mg per deciliter despite receiving the maximum tolerated dose of statins — the addition of ezetimibe is reasonable. If the LDL cholesterol level is still 70 mg per deciliter or higher, a PCSK9 inhibitor can be added.[4]

For patients 75 years of age or older, initiation

or continuation of a moderate- or high-intensity statin is reasonable. The statin dose may need to be reduced in patients at risk for adverse effects from polypharmacy and altered pharmacokinetics.

OVERVIEW OF LIPID-LOWERING DRUGS

STATINS

Statins remain the primary pharmacotherapy used to lower LDL cholesterol levels. Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which affects the rate-controlling step in cholesterol synthesis[27] (Fig. 1). Inhibition of HMG-CoA reductase leads to increased expression of the hepatic LDL receptor and increased clearance of LDL from the circulation.

Meta-analyses of randomized, controlled trials have reported that for every reduction of 39 mg per deciliter (1.0 mmol per liter) in LDL cholesterol level, statins confer relative reductions in cardiovascular events and all-cause mortality of 22% and 10%, respectively.[2,28] More intensive statin regimens conferred a reduction in major adverse cardiovascular events that was 15% greater than that conferred with less intensive regimens.[2] Trials focused exclusively on primary prevention reported similar and significant relative reductions in fatal or nonfatal atherosclerotic cardiovascular disease events.[3]

For the vast majority of patients in whom statins are indicated, the benefits outweigh the risks.[29] The risk of serious muscle injury, including rhabdomyolysis, associated with statins is very low (<0.1%) and the risk of serious liver injury is even lower (approximately 0.001%). There is a modest increase in the risk of diabetes mellitus of 0.2% per year (depending on the person's baseline risk for diabetes), but the benefits of statins generally also outweigh risks for patients with diabetes.

There is controversy regarding the extent of myalgia that is related to statins. The rate of myalgia is low in blinded randomized trials,[29] although these trials generally have a run-in phase to screen for side effects. Higher rates of myalgia are reported more frequently in clinical practice,[30,31] but it remains uncertain how frequently the symptoms reported are truly attributable to statins or to "nocebo" effects, in which patients may perceive side effects of medications that are actually caused by anticipation of negative effects.[31] An ongoing study, SAMSON (Self-Assessment Method for Statin Side Effects or Nocebo; ClinicalTrials.gov number, NCT02668016), may offer more insights.

Once initiated, statins should generally be continued long-term. The benefits are greater in the second, third, and fourth years than in the first year. In long-term follow-up of the West of Scotland Coronary Prevention Study, 5 years of statin treatment were reported to confer a 20-year legacy of continued benefit.[32]

EZETIMIBE

Ezetimibe blocks the Niemann–Pick C1-like 1 cholesterol transfer protein to inhibit intestinal and biliary cholesterol absorption, leading to an increase in the expression of hepatic LDL receptors[27] (Fig. 1). In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), among patients with acute coronary syndrome whose LDL cholesterol levels were less than 125 mg per deciliter (3.2 mmol per liter), the addition of ezetimibe to simvastatin conferred a significant reduction in the absolute risk of recurrent cardiovascular events of 2 percentage points (constituting a 6% reduction in relative risk).[15] This finding translates to a number needed to treat of 50 to prevent 1 major cardiovascular event over 7 years. The median LDL cholesterol level achieved was 54 mg per deciliter (1.4 mmol per liter) in the group receiving simvastatin and ezetimibe as compared with 70 mg per deciliter with simvastatin alone, providing evidence of additional benefit with further lowering of LDL cholesterol level.[33] Ezetimibe is used in patients who have unacceptable side effects with statins, who have severe primary hypercholesterolemia, or who have insufficient reduction in LDL cholesterol levels when taking the maximum tolerated statin dose. Because no outcomes trial has shown benefit with ezetimibe when used in isolation, those who take ezetimibe because of statin intolerance should continue to take the maximum tolerated statin dose.

PCSK9 INHIBITORS

Gain-of-function mutations in *PCSK9* are a cause of familial hypercholesterolemia,[34] and loss-of-function mutations are associated with a phenotype of lower LDL cholesterol levels and a lower risk of coronary heart disease than are found in

persons who do not have loss-of-function mutations.[35] The PCSK9 enzyme binds to the LDL receptor to promote its internal hepatic degradation. PCSK9 inhibitors are subcutaneously injected monoclonal antibodies that inactivate the PCSK9 enzyme, which in turn increases the availability of LDL receptors on hepatocytes, thereby promoting the removal of LDL cholesterol from the circulation (Fig. 1). The result is a dramatic reduction in LDL cholesterol levels of approximately 60%.[16,36] The PCSK9 inhibitor evolocumab also lowers mean lipoprotein(a) levels by 27%.[37]

The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial[16] enrolled more than 27,000 persons with stable atherosclerotic cardiovascular disease and an LDL cholesterol level of 70 mg per deciliter or higher or a non-HDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or higher despite receipt of moderate- or high-intensity statin therapy. Participants were randomly assigned to receive evolocumab or placebo. The primary outcome was death from cardiovascular causes, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Over a median of 2.2 years, the median LDL cholesterol level declined to 30 mg per deciliter (0.8 mmol per liter) in persons receiving evolocumab. They also had a rate of major adverse cardiovascular events that was 1.5 percentage points lower than the rate among those who were not taking evolocumab, corresponding to a relative reduction in events of 15%.[16] The absolute reductions in risk conferred by evolocumab were greater among those who had a higher absolute risk of these events, such as persons with peripheral artery disease,[38] a history of recent or multiple myocardial infarctions,[39] or elevated lipoprotein(a) levels.[37] However, no significant reduction in mortality was seen over this short-term follow-up period.

The ODYSSEY OUTCOMES trial tested the benefit of alirocumab in patients who had had an acute coronary syndrome within the past year and who had an LDL cholesterol level of at least 70 mg per deciliter, a non-HDL cholesterol level of at least 100 mg per deciliter, or an apolipoprotein B level of at least 80 mg per deciliter despite taking the maximum tolerated dose of a statin.[36] Nearly 19,000 patients were randomly assigned to receive alirocumab or placebo and were followed for the primary outcome of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for angina. The trial included a dose-adjustment strategy to reach an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). Over a median of 2.8 years, the mean LDL cholesterol level in patients receiving alirocumab was 38 mg per deciliter (1.0 mmol per liter). They also had a significant absolute reduction in risk of 1.6 percentage points, representing a relative reduction of 15%, for the primary outcome of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for angina. There was also an absolute reduction in risk of 0.6 percentage points in all-cause mortality, representing a 15% reduction in relative risk. The reduction in all-cause mortality did not reach the prespecified definition for statistical significance.[36]

PCKS9 inhibitors are used for high-risk patients (for secondary prevention or severe primary hypercholesterolemia) who have adverse reactions to statins or who have an insufficient reduction in LDL cholesterol level while taking the maximum tolerated dose of a statin plus ezetimibe. There appears to be a linear relationship between reduced LDL cholesterol level and lower cardiovascular risk, even down to LDL cholesterol values of less than 10 mg per deciliter (0.3 mmol per liter), with no early signal for harm associated with very low LDL cholesterol levels.[40] Safety beyond 3 years is not yet well established, and PCSK9 inhibitors may not be reasonably cost-effective for the average patient until the annual cost falls below $5,500.[41] Burdensome preauthorization procedures have been a barrier to access to this therapy for many patients.[42]

n–3 Fatty Acids

Long-chain n–3 polyunsaturated fatty acids, which can be a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid or EPA alone, reduce triglyceride levels by reducing production of very-low-density lipoprotein (VLDL) cholesterol in the liver and to a lesser extent by increasing VLDL cholesterol clearance from the circulation. Patients with severe hypertriglyceridemia (triglyceride level >500 mg per deciliter [5.6 mmol per liter]) typically need to be treated with 4 g per day of n–3 fatty acids to reduce triglyceride levels by 20 to 30%.[43]

Early open-label trials, including GISSI (Gruppo Italiano per lo Studio della Sopravvivenza

nell'Infarto Miocar dico)–Prevenzione[44] and JELIS (Japan Eicosapentaenoic Acid Lipid Intervention Study)[45] suggested benefit from n–3 fatty acids for reduction of the risk of coronary heart disease. However, two recent meta-analyses, which included randomized, controlled trials published through 2017, reported no significant reduction in vascular events with n–3 therapy.[46,47] Neither the VITAL (Vitamin D and Omega-3) trial[48] nor ASCEND (A Study of Cardiovascular Events in Diabetes),[49] published in 2019 and 2018, respectively, reported a benefit from the use of n–3 therapy at a dose of 1 g per day with respect to the primary composite outcome of major adverse cardiovascular events.

In contrast, in REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial), the risk of major adverse cardiovascular events was significantly lower, by 25%, among patients who received 4 g of icosapent ethyl daily than among those who received placebo.[50] REDUCE-IT enrolled patients with high baseline risk (known atherosclerotic cardiovascular disease or diabetes mellitus plus at least one additional vascular risk factor) who had LDL cholesterol levels that were controlled with statin therapy but who had elevated triglyceride levels (135 to 500 mg per deciliter [1.5 to 5.6 mmol per liter]). Icosapent ethyl is a proprietary and highly purified form of EPA, and the findings from REDUCE-IT should not be generalized to apply to recommendations regarding dietary supplementation with fish oil.

Because the reduction in cardiovascular risk seen with icosapent ethyl exceeded the anticipated benefits from the observed reduction in triglyceride levels (approximately 20%), other potentially beneficial mechanisms, such as antiinflammatory or antithrombotic effects, have been entertained. The use of icosapent ethyl for the prevention of cardiovascular events was not discussed in the guidelines on cholesterol management published by the ACC–AHA in 2018,[4] but this therapy may play a key role in future recommendations for the prevention of cardiovascular disease once confirmatory studies have been published. In the ongoing STRENGTH (Outcomes Study to Assess Statin Residual Risk Reduction with EpaNova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial (NCT02104817), researchers are evaluating whether n–3 carboxylic acids, prescribed at a dose of 4 g per day, can reduce the rate of major cardiovascular events in patients with hypertriglyceridemia and low HDL cholesterol levels, despite controlled LDL cholesterol levels.

OTHER AGENTS

The development of the medications discussed above has led to a decline in the use of older agents, such as fibrates, niacin, and bile-acid sequestrants, which were previously mainstays of lipid management. These agents, as well as restricted-use therapeutics reserved for the treatment of severe lipid disorders, are discussed in the Supplementary Appendix.

EMERGING APPROACHES

Inclisiran is a small interfering RNA designed to target PCSK9 messenger RNA and thus inhibit PCSK9 synthesis.[51] It has the potential benefit of far lower dose frequency than treatment with monoclonal antibodies to PCSK9. A phase 2 randomized trial in which inclisiran was compared with placebo showed dose-dependent reductions in PCSK9 and LDL cholesterol levels.[52] ORION-4 (A Randomized Trial Assessing the Effects of Inclisiran on Clinical Outcomes among People with Cardiovascular Disease; NCT03705234) is a large, ongoing, phase 3 trial investigating whether inclisiran can reduce major cardiovascular events in adults with established cardiovascular disease.

Bempedoic acid is an inhibitor of ATP citrate lyase that up-regulates LDL receptors by reducing cholesterol synthesis.[51] The active metabolite requires an enzyme not thought to be present in myocytes, so the absence of side effects that affect muscle is a potential benefit of this drug as compared with statins. In the CLEAR Harmony (Evaluation of Long-Term Safety and Tolerability of ETC-1002 in High-Risk Patients with Hyperlipidemia and High Cardiovascular Risk) trial, patients who received maximally tolerated statin therapy administered with bempedoic acid had significantly lower LDL cholesterol levels than those who received placebo (mean difference, 18%), without an increase in serious adverse events.[53] The efficacy and safety of bempedoic acid will be further determined in a larger cardiovascular outcome trial, CLEAR-OUTCOMES (Evaluation of Major Cardiovascular Events in Patients with, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated

with Bempedoic Acid [ETC-1002] or Placebo; NCT02993406), which is enrolling 12,600 patients at high cardiovascular risk who have adverse effects in response to statins and have an LDL cholesterol level of 100 mg per deciliter or higher.

AKCEA-APO(a)-L_{Rx} is an antisense oligonucleotide drug targeting lipoprotein(a) that can reduce lipoprotein(a) levels by up to 90% and appeared to be safe in phase 2 trials (e.g., Phase 2 Study of ISIS 681257 [AKCEA-APO(a)-LRx] in Patients with Hyperlipoproteinemia[a] and Cardiovascular Disease; NCT03070782).[51] It is planned to be evaluated next in a phase 3 cardiovascular outcomes trial. Also under study are drugs targeting angiopoietin-like 3 (ANGPTL3), either with monoclonal antibodies or antisense oligonucleotides, which have shown promise in early-phase trials.[51,54] ANGPTL3 is an inhibitor of lipoprotein lipase; thus inhibition of ANGPTL3 lowers levels of triglycerides and LDL cholesterol.[51] A phase 2 study of an antisense drug that targets apolipoprotein C3 (NCT03385239), involving patients with hypertriglyceridemia, has also been completed.

ADDITIONAL CONSIDERATIONS

The 2018 cholesterol guidelines recommend measurement of lipid levels every 4 to 12 weeks after the initiation of a statin or dose adjustment to assess patient adherence to the prescription and the extent of reduction in the LDL cholesterol level.[4] Subsequently, periodic measurement of lipids (every 3 to 12 months) is reasonable. For most patients, fasting is not required before testing, although a fasting lipid profile may be still be beneficial in the evaluation of genetic hyperlipidemia, premature atherosclerotic cardiovascular disease, or persistent hypertriglyceridemia.

Statin intolerance is defined as the inability to receive at least two different statins, including one administered at the lowest starting daily dose. Several publications have provided more detailed guidance on how to approach the treatment of patients with statin intolerance,[55,56] which typically includes a review of drug–drug interactions and of other health conditions that can cause muscle-related symptoms and discontinuation of the statin, with subsequent rechallenge (ideally with the use of a statin with pharmacokinetics that are different from those of the initial statin) to verify muscle-related symptoms.

The 2018 cholesterol guidelines have incorporated LDL cholesterol thresholds for the addition of nonstatin therapy to statin therapy[4]; however, it is noteworthy that the Friedewald equation, which is used to estimate LDL cholesterol levels, can be inaccurate when LDL cholesterol levels are very low[57] or when triglyceride levels are elevated. The Martin–Hopkins LDL cholesterol estimation is an "adaptable" method that is used to gauge the LDL cholesterol level by applying an adjustable factor for the ratio of triglycerides to VLDL cholesterol (www.hopkinsmedicine.org/apps/all-apps/ldl-cholesterol-calculator). It is more accurate than the Friedewald method, particularly for those with elevated triglyceride levels[58] or low LDL cholesterol levels; it also performs better on nonfasting samples.[59]

Although this review focuses on the guidelines put forth by the ACC–AHA, it is important to note that other guidelines have been published separately by the U.S. Preventive Services Task Force,[60] the Department of Veterans Affairs,[61] the National Lipid Association,[62] the American Association of Clinical Endocrinologists,[63] and the European Society of Cardiology–European Atherosclerosis Society[64] (reviewed in Table S2). These guidelines also endorse statins for use in secondary and primary prevention for patients at high risk for cardiovascular events (with the decision to initiate or adjust pharmacotherapy made on the basis of absolute risk of cardiovascular disease), but there are differences between these guidelines and the 2018 ACC–AHA guidelines, such as the 10-year-risk estimation cutoff points used to classify levels of elevated risk, the intensity of the statin recommended, and the LDL cholesterol thresholds for treatment.

CONCLUSIONS

Management of serum cholesterol is a central objective in the effort to prevent atherosclerotic cardiovascular events. A discussion of cardiovascular risk is warranted in all patients. Lifestyle changes targeted at improving a patient's lipid profile form the foundation for prevention, along with management of other cardiovascular risk factors.[5,65,66] For patients whose risk of cardiovascular disease is sufficiently elevated to suggest a net benefit, pharmacologic treatment with statins is recommended, with the intensity of treatment matching the absolute baseline level of cardiovascular risk. For patients at high risk

who have not had the anticipated reduction in LDL cholesterol level of 50% or more or who have a residual LDL cholesterol level of 70 mg per deciliter or higher despite therapy with the maximum tolerated dose of a statin, ezetimibe, with or without a PCSK9 inhibitor, may be considered for secondary prevention. High-dose EPA has emerged as a promising therapy for additional cardiovascular event reduction among patients taking statins who have residual elevation in triglyceride levels. New therapies for lowering lipid levels are showing promising results in early clinical trials and are awaiting confirmation of benefit and safety in large cardiovascular outcome studies. The results of these studies may change the ways in which lipids are managed in the future.

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